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Case Report

Thiamine pyrophosphokinase deficiency causes a Leigh Disease like phenotype in a sibling pair: identification through whole exome sequencing and management strategies[☆]

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ABSTRACT

We present a sibling pair with Leigh-like disease, progressive hypotonia, regression, and chronic encephalopathy. Whole exome sequencing in the younger sibling demonstrated a homozygous thiamine pyrophosphokinase (TPK) mutation. Initiation of high dose thiamine, niacin, biotin, α-lipoic acid and ketogenic diet in this child demonstrated improvement in neurologic function and re-attainment of previously lost milestones. The diagnosis of TPK deficiency was difficult due to inconsistent biochemical and diagnostic parameters, rapidity of clinical demise and would not have been made in a timely manner without the use of whole exome sequencing. Molecular diagnosis allowed for attempt at dietary modification with cofactor supplementation which resulted in an improved clinical course.

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1. Introduction

Thiamine pyrophosphate (TPP) is a required cofactor for the mitochondrial enzyme complexes pyruvate dehydrogenase, α -ketoacid dehydrogenase, and branched chain ketoacid dehydrogenase. It is also required for the cytosolic transketolase and the peroxisomal α -oxidation of 3-methyl-branched and straight chain 2-hydroxy long chain fatty acids by 2-hydroxyacyl-CoA lyase 1. TPP is synthesized by the enzyme thiamine pyrophosphokinase (TPK) [1–17]. Mayr et al. demonstrated that patients with autosomal recessive mutations in TPK can present with variable degrees of encephalopathy, developmental delay and hypotonia [18]. In their cohort, illness and other causes of increased catabolism triggered acute decompensation. The individuals with TPK mutations had motor dysfunction particularly related to striatal, basal ganglial, and cerebellar regions of the brain, but cognition appeared to remain intact [18]. In the three families previously reported, the range of symptomatic presentation was between 18 months and 4 years. Thiamine supplementation was attempted in three out of five patients. Two of those were reported to have stabilization of symptoms with some improvement in function. One child was placed on a 70% fat containing diet. Laboratory analyses obtained in this cohort noted consistent elevations in α -ketoglutaric acid [18].

2. Case series

Here we describe the clinical presentation and care of a sibling pair, born to consanguineous second-cousins of Chinese descent.

2.1. Patient 1

P1 was born via cesarean section for fetal decelerations at term. Initial developmental delay and hypotonia were noted at 7 months of age with slow developmental progress until 26 months, when she developed a febrile illness and rapidly regressed in both motor and cognitive milestones. At 28 months of age she was admitted to hospital for increasing fatigue, weakness, decreased oral intake, lethargy, and intractable seizures with severe and rapid progression to coma. She died at 29 months secondary to multi-organ failure after having suffered multiple metabolic strokes in the setting of metabolic collapse.

Cerebral MRI at 12 months of age demonstrated T2 bright abnormalities (Fig. 1, A–C) in the basal ganglia and thalami. Repeat MRI during her metabolic collapse at 28 months revealed progressive findings suggestive of mitochondrial disease (Fig. 1, D–F).

Pre- and post-mortem laboratory evaluations were extensive. Cytogenetic, molecular and biochemical analyses included karyotype, mitochondrial DNA mutation and deletion analysis, plasma amino acids, electron transfer analysis via muscle biopsy, pyruvate carboxylase and pyruvate dehydrogenase levels from post mortem fibroblast analyses. All the studies were non-diagnostic. Urine organic acids demonstrated elevations in lactic, α -ketoglutaric and fumaric acids. Thiamine levels were not obtained during her clinical decompensation or post-mortem studies.

2.2. Patient 2

P2 was born at 38 weeks of gestation via repeat cesarean section after an uneventful pregnancy. Initial evaluation at two weeks was without concern as he was breast-feeding well, with normal tone and neurologic exam. By four months, his exam demonstrated mild hypotonia, episodic extremity stiffening and a decreased level of alertness.

By 12 months of age, his hypotonia progressed with inconsistent head control, inability to sit without support, and persistent drooling with poor oral intake. A cranial MRI with sedation was obtained at this time and revealed T2 abnormalities similar to his sibling (Fig. 1, G–I). At 18 months he was admitted to the hospital because neurological decline. His exam was notable for complete loss of head control, bulbar dysfunction, fatigue, weakness, worsening hypotonia, and persistent food refusal except for very small quantities of a traditional Chinese rice porridge. Immediately upon admission, additional biochemical laboratory evaluation was performed, and aggressive management of his fluid and nutritional status was initiated because of his sister's rapid metabolic decompensation prior to her death. Laboratory analyses included interpretations of plasma amino acids, acylcarnitine profile, lactate, pyruvate and very long chain

fatty acids, which were all non-diagnostic. As in P1, urine organic acids demonstrated elevations of α -ketoglutarate and glutaric acids. Mild lactic acidosis was present but easily resolved with rehydration.

Due to the history of consanguinity and similar clinical presentation as his sibling, whole exome sequencing (WES) was pursued. Results were available concurrent to the 18 month admission, and a diagnosis of thiamine pyrophosphokinase (TPK) deficiency was made. TPP levels were not available due to insurance regulations prior to or following admission. As the sibling's muscle biopsy was not diagnostic, consideration for additional muscle and skin biopsies were felt to be of marked risk and were not pursued due to the history of neurologic decline with anesthesia after the cranial MRI. Medical therapy was initiated.

2.3. Molecular diagnosis

Whole exome sequencing (WES) performed in a CLIA-approved laboratory revealed a homozygous missense mutation in TPK (*606370) (c.604 T>G; p.W202G). This mutation is located in the thiamine binding domain, in a moderately conserved nucleotide and highly conserved amino acid, and is predicted to be pathogenic by in-silico analyses using PolyPhen, SIFT, and Alamut. Both parents are heterozygous for the mutation. Confirmatory testing on residual post mortem DNA from P1 revealed that she was also homozygous for the same mutation.

2.4. Therapeutic strategy

Because of his neurologic regression and the severity of his sister's presentation, P2 was treated with a generalized and aggressive approach of both diet modification and cofactor supplementation. The working hypothesis was that TPK1 deficiency possibly affected the TCA cycle. Supplementation included thiamine (10 mg/kg, 3 times per day) with the assumption there was some residual TPK enzyme activity. Additionally, niacin (10 mg/kg, 3 times per day), biotin (5 mg, 3 times per day), and α -lipoic acid (5 mg/kg, 3 times per day) were initiated to provide further cofactor support for other presumably affected metabolic pathways. Ketogenic diet (Ketocal 3:1) via nasogastric tube feeding was initiated to reduce metabolic demand through pyruvate dehydrogenase (PDH). The premise of this therapy was to factor in the consumption of TPP required for normal function of PDH in a standard, carbohydrate-prominent diet. After almost nine months on this diet modification, both the cofactor supplements and ketogenic diet continue to be well tolerated and the family is extremely hesitant to change any medical intervention at this time.

2.5. Clinical progress following therapeutic intervention

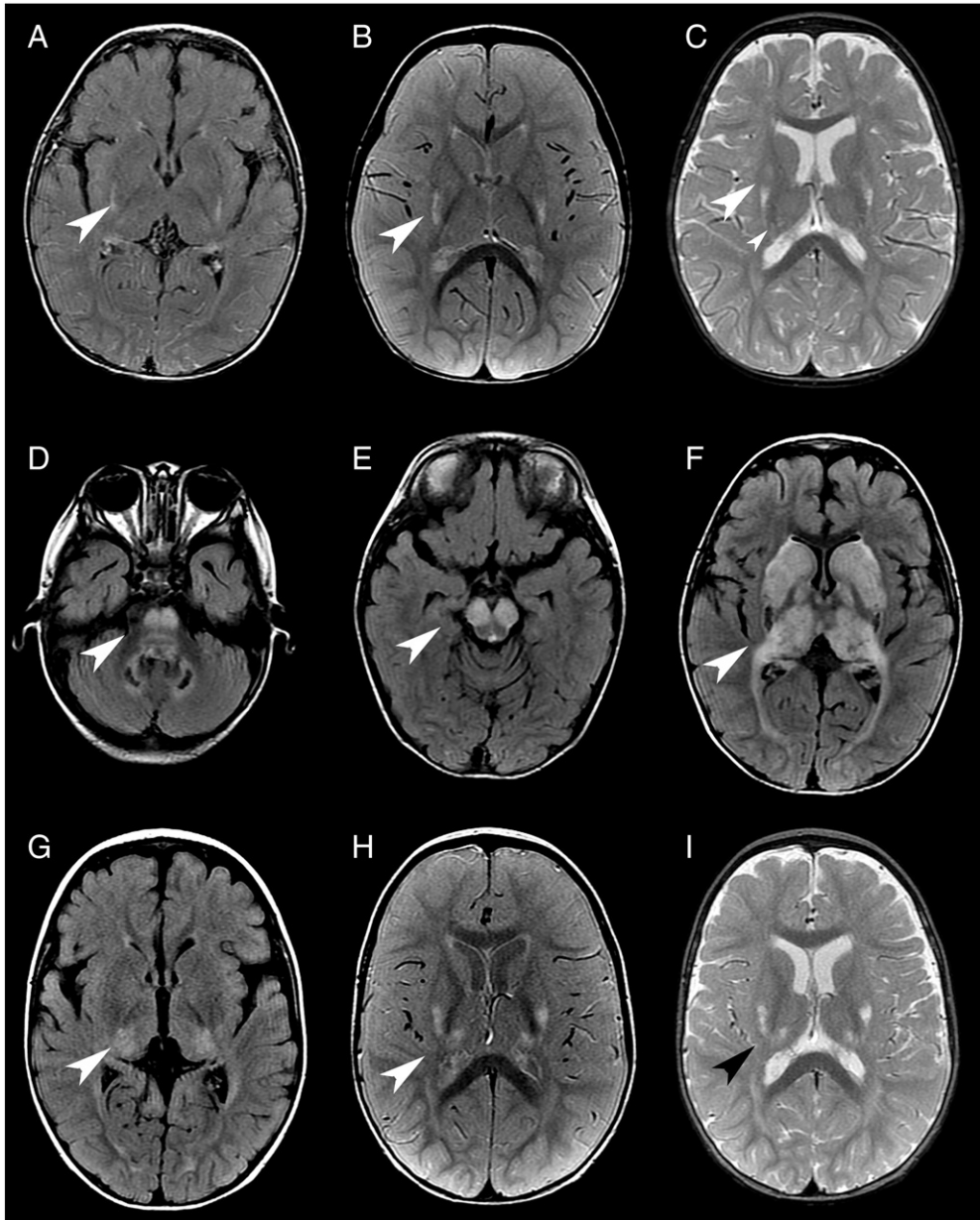
Since initiation of therapy, P2, now 29 months old, has demonstrated markedly improved head control, stability of truncal tone, increased verbal response and social interaction. He is not able to walk, but is able to stand with support. Though most of the diet is provided via a nasogastric tube, he is now able to supplement with oral intake in small quantities, point to his body parts, and maintain a sitting position. During a recent viral illness, oral intake decreased and bulbar signs (drooling and lethargy) were transiently present, but did not persist after resolution of the illness. Administration of live virus vaccines (measles, mumps, and rubella (MMR) and varicella) had been postponed due to concerns over possible concurrent decompensation. He tolerated vaccination with killed, acellular vaccines (including influenza) during a controlled hospitalization with intravenous hydration. Analysis of urine organic acids revealed lactate, ketone and TCA cycle moieties which were identical just prior to and 24 h after vaccine administration. In comparison, the levels of these moieties were also similar to those obtained when he was clinically well.

3. Discussion

Currently, whole exome sequencing remains the only clinically available molecular testing modality for TPK deficiency. Based upon the experiences with this family, the diagnosis is likely under-recognized as a cause of Leigh-like encephalopathy. These siblings are the youngest reported with TPK deficiency and have

the most severe presentation with rapid and progressive neurologic decline. Biochemical analysis of TPP quantitation and TPP: total thiamine ratios could be utilized to suggest an underlying deficiency but are not clinically available in this country, and may not allow for a diagnosis in time for clinical management. While biochemical testing in this family and the cohort of Mayr et al. revealed an elevation of α -ketoglutarate in the urine, P2's serial analyses of urine organic acids and α -ketoglutarate during the initiation of diet, febrile illness, and vaccine administration were not correlative to his clinical examination and could not be used to monitor medical management.

The molecular diagnosis in this family helped to provide a definitive diagnosis in a time frame that allowed for an attempt at dietary intervention. It was also directive for appropriate genetic counseling of



affected and carrier family members. This is the first report of use of dietary management in the setting of cofactor supplementation to improve a clinical outcome in a patient with severe TPK mutations. These experiences suggest that patients with elevation of urinary α -ketoglutarate and phenotypic similarity to this family should be considered for molecular diagnosis of TPK deficiency.

Conflict of interest

None

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Fig. 1. MRI findings in sibling pair with TPK deficiency. A–C, MRI of Patient 1 at 11 months of age. Axial FLAIR (A), proton density (B) and T2 (C) images at the level of the thalamus. The images demonstrate increased signals in the posterior aspect of the putamen bilaterally (large arrowheads), and subtle changes in the ventrolateral thalamus (small arrowhead, C). Myelination was normal for age. D–F, MRI of Patient 1 at 28 months. Axial FLAIR images at the level of the lower pons (D), the midbrain (E), and the thalami (F). Increasing T2 signal abnormalities have developed, involving bilateral caudate, putamen, globus pallidus, thalami and optic radiations (arrowhead, F). The corticospinal tracts traveling through the midbrain, pons and medulla are involved (arrowheads, D and E), with additional abnormal signals in the posterior pontine tracks and deep cerebellum (D). Restricted diffusion with signal changes was present in the caudate, putamen and globus pallidus, as well as parts of the thalami and corticospinal tract (not illustrated). G–I, MRI of Patient 2 at 12 months of age. Axial T2 FLAIR (G), spin echo proton density (H) and T2 (I) images. The extent of myelination is advanced for age. Abnormal hyperintense T2 signal is evident in the posterior putamina and thalami (arrowheads) bilaterally. Abnormal signal in the dentate nuclei was present (not illustrated). MR Spectroscopy over the basal ganglia demonstrated nonspecific increase in the choline to creatine ratio with no lactate peak, and diffusion images were normal (not illustrated). Findings are similar in pattern and distribution to his sibling's.